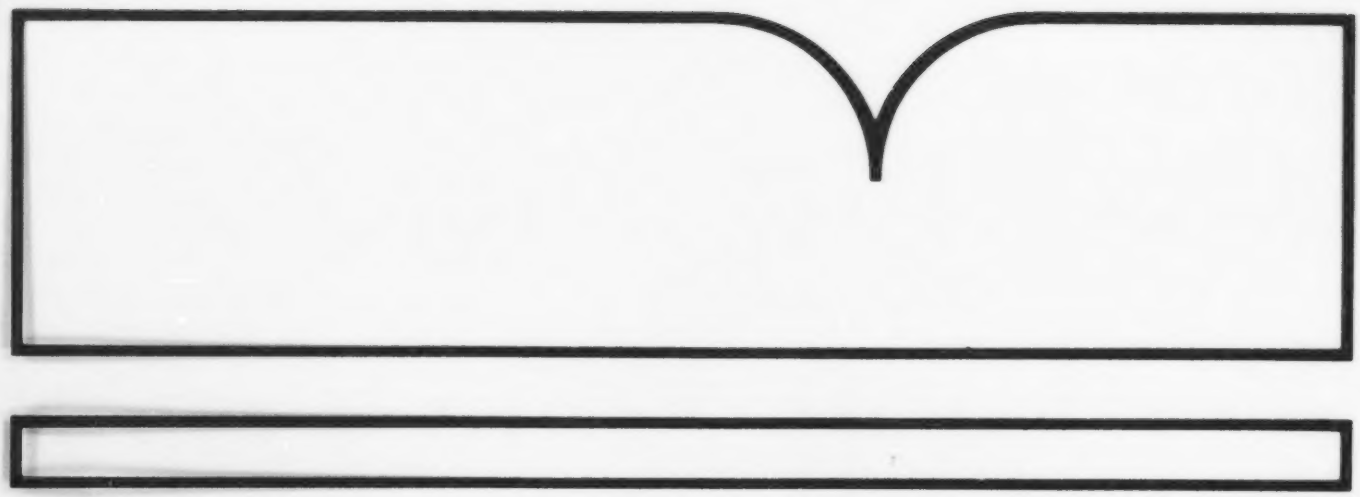
PB88-162219

Pesticide Assessment Guidelines Subdivision F, Hazard Evaluation: Humans and Domestic Animals. Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90 Day Study) Addendum 5 on Data Reporting

(U.S.) Environmental Protection Agency
Washington, DC

Jan 88



U.S. Department of Commerce
National Technical Information Service
NTIS

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3 PB88-162219

4. Title and Subtitle
ADDENDUM 5 ON DATA REPORTING TO PESTICIDE ASSESSMENT GUIDELINES
Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90-Day Study)

5. Report Date
January 1988

6.

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8. Performing Organization Rept. No.
540/09-88-029

9. Performing Organization Name and Address
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10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Same as #9

13. Type of Report & Period Covered

14.

15. Supplementary Notes
Addendum 5 to Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals (EPA 540/9-82-025 and NTIS Order Number PB83-153916), October, 1982

16. Abstract (Limit: 200 words)

The Data Reporting Guideline (DRG) for Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90-Day Study), Series 81-7 and 82-5, gives guidance to pesticide registrants on the format of their study report so that the Agency can review it efficiently. This guidance clarifies sections in the existing Pesticide Assessment Guidelines, Subdivision F, on data reporting. It provides an outline for the study report which data submitters can use in preparing their reports for submission to EPA to meet 40 CFR 158 data requirements for the registration of pesticides.

The DRG for Series 81-7 and 82-5, Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90-Day Study), is only one of a number of DRGs published by the National Technical Information Service as an addendum to Subdivision F of the Pesticide Assessment Guidelines.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

c. COSATI Field/Group

18. Availability Statement
Unclassified and freely available

19. Security Class (This Report)
Unclassified

21. No. of Pages
10

20. Security Class (This Page)
Unclassified

22. Price
A02 9.95

540/09-88-029

PESTICIDE ASSESSMENT GUIDELINES

SUBDIVISION F

HAZARD EVALUATION:

HUMANS AND DOMESTIC ANIMALS

Series 81-7 and 82-5

Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90-Day Study)

ADDENDUM 5 ON DATA REPORTING

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Subdivision F - Acute Delayed Neurotoxicity of Organophosphorous Substances and Subchronic Delayed Neurotoxicity (90-Day Study)

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PESTICIDE ASSESSMENT GUIDELINES

HUMANS AND DOMESTIC ANIMALS

Acute Delayed Neurotoxicity of Organophosphorous Substances and Delayed Subchronic Neurotoxicity (90-Day Study)

Subdivision F, Series 81-7 and 82-5

DATA REPORTING

INTRODUCTION

A. Purpose

The purpose of this document is to provide guidance in submitting reports of studies on the Acute Delayed Neurotoxicity of Organophosphorous Substances and Delayed Subchronic Neurotoxicity (90-Day Study) [Subdivision F, §81-7 and 82-5].

B. Objective

The objective of these guidelines is to provide an acceptable format for reporting materials, methods, and results of neurotoxicity studies. Data submitters are encouraged to submit complete reports for efficient review by the Agency. This guideline pertains to organizing and presenting the substance of the data report. PR Notice 86-5, effective November 1, 1986 and available from the Office of Pesticide Programs, US EPA, pertains to the physical formatting of reports which are referred to as "studies" and submittal packages. Some of its requirements are mandatory.

RESPONSE TO PUBLIC COMMENTS

Two comments were received in response to the public notice published in the FEDERAL REGISTER of March 25, 1987 (52 FR 9536). The Agency has considered the comments and revised the document in response to some of these comments. Responses to specific comments are provided below for the benefit of data submitters.

Comment - I. SUMMARY:

If this part of the document is to "stand alone" it should perhaps contain a brief description of study design and methods. This is not clear as given in the document. It is normal procedure to split the summary into methods and results.

Response:

The comment is germain and the "SUMMARY" description has been modified to reflect this.

Comment - Test Report:

The time of death is perhaps too specific as in many cases it is impossible to say other than the bird died overnight.

Response:

The phrase has been changed to "time or day of death".

Comment - Test Report:

Is it really necessary to give a detailed description of all histopathological findings. A tabular presentation for lesions scores is clearer with the results summarized in a discussion section.

Response:

Exerience in evaluating reports of neurotoxicity studies from the commenter have shown that the "lesion score" method is sufficient for this type of study. It is a reporting method which allows numerical comparison of results between experimental groups. It must be noted that a detailed description of the scoring system and a discussion of the results is necessary when using this system or any system. The section has been modified to include this approach.

Comment - Test Report for Subchronic Neurotoxicity:

This section is not consistant with the acute delayed neurotoxicity report format.

Response:

For consistancy, the same items have been included in both acute and subchronic reports.

Comment - DISCUSSION:

Is a Discussion section mandatory?

Response:

No, a discussion is necessary only when there is something to discuss.

Comment - APPENDIX(CES):

The requirement to include historical control data is new and is not clear. Are we refering to negative and/or positive control data and is it mandatory? Clarification on this point would be appreciated.

Response:

Since the specific abnormality and associated pathological lesion are not observed in nature, the requirement for historical control data is

not relevent and has been removed. Concurrent negative and positive control groups provide the necesssary control data.

Comment - APPENDIX(CES):

By inference, analysis of test formulation/diets is required for both studies.

Response:

The analysis applies to both studies for the test substance and to the subchronic study for the test diet (only if the material is administered in the diet).

GUIDELINE

The Final Report should contain the following items.

COVER PAGE

Cover page and additional documentation requirements (i.e., requirements for data submission, Good Laboratory Practice statement, and statement of data confidentiality claims), if relevant to the study report, must precede the content of the study formatted below. These requirements are described in PR Notice 86-5.

TABLE OF CONTENTS

This item should be a concise listing of the essential elements of the Final Report including the page numbers for each. Essential elements should include a Summary, an Introduction, Materials and Methods, Results, Discussion, Bibliography, Tables, Figures, Appendices, and key subsections as appropriate.

BODY OF THE REPORT

This item shall include all information required in §80-4(b)(2), §80-4(c), §81-7 and §82-5(c) of this Subdivision. Additional recommendations are provided in paragraphs identified as III and IV of this addendum.

I. SUMMARY

As per §80-4(b)(1) of this Subdivision, this section of the test report shall contain a summary of the experimental design, methods, and results, an analysis of the data, and a statement of the conclusions drawn from the analysis. The summary should highlight any and all positive data or observations, and any deviations from control data which may be indicative of toxic effects.

II. INTRODUCTION (include the objectives of the study)

III. MATERIALS/METHODS

This section of the Final Report shall include information required by §80-4 of this Subdivision.

IV. RESULTS

Acute Neurotoxicity 81-7: Data and Reporting.

A. Treatment of Results

Data shall be summarized in tabular form, showing for each test group the number of animals at the start of the test, the number of animals showing lesions or effects, the types or grades of lesions or effects and the percentage of animals displaying each type of lesion or effect.

B. Evaluation of Results

The findings of an acute delayed neurotoxicity study shall be evaluated in terms of the incidence and severity of neurotoxic effects and of any other observed effects and histopathological findings in the treated and control groups.

C. Test Report

The test report shall include the following information:

1. Doses administered (mg/kg);
2. Toxic response data by group with a description of clinical manifestations of nervous system damage (where a grading system is used, the criteria should be defined);
3. For each animal, time or day of death during the study or whether it survived to termination;
4. The day of observation of each abnormal sign and its subsequent course;
5. Body weight data;
6. Necropsy findings for each animal, when performed;
7. A detailed description of all histopathological findings (a defined grading or scoring system may be used); and
8. Statistical treatment of results, where appropriate.

Subchronic Neurotoxicity 82-5: Data and Reporting.

A. Treatment of Results

Data shall be summarized in tabular form, showing for each test group the number of animals at the start of the test, the number of animals showing lesions or effects, the types or grades of lesions or effects, and the percentage of animals displaying each type of lesion or effect.

B. Evaluation of Results

The findings of a subchronic delayed neurotoxicity study should be evaluated in conjunction with the findings of preceding studies and considered in terms of the incidence and severity of observed neurotoxic effects and any other observed effects and histopathological findings in the treated and control groups. A properly conducted subchronic test should provide a satisfactory estimation of a no-effect level based on lack of clinical signs and histopathological changes.

C. Test Report

The test report shall also include the following information:

1. Doses administered (mg/kg);

2. Toxic response data by group with a description of clinical manifestations of nervous system damage (where a grading system is used, the criteria should be defined);

3. For each animal, time or day of death during the study or whether it survived to termination;

4. The day of observation of each abnormal sign and its subsequent course;

5. Body weight data;

6. Necropsy findings for each animal, when performed;

7. A detailed description of all histopathological findings (a defined grading or scoring system may be used); and

8. Statistical treatment of results, where appropriate.

V. DISCUSSION (optional)

VI. BIBLIOGRAPHY

This item should contain a list of references cited in the body of the report.

VII. VERIFICATION

This item shall contain information required by §80-4(b)(2). Each test report shall be:

A. Signed by each of the senior scientific personnel, including the laboratory director responsible for performing and supervising the testing, preparing, reviewing, and approving the test report; and

B. Certified by the applicant or an authorized agent of the applicant as a complete and unaltered copy of the report provided by the testing laboratory whether independent or owned, operated, or controlled by the applicant.

VIII. ARCHIVES

This section of the Final Report shall contain all information required in 40 CFR 160.185.

IX. TABLES/FIGURES

X. APPENDIX(ES)

These should include individual animal data, pathology report, analytical method and results of analyses on the test substance and test diet (if the material is administered via the diet), details of statistical analyses, and other information as appropriate.